



## EDITORIAL

# Utility and limitations of *T. gondii*-specific IgM serum antibodies in the diagnosis of congenital toxoplasmosis in Porto Alegre ☆,☆☆



## Utilidade e limitações de anticorpos séricos IgM específicos contra o *T. gondii* para o diagnóstico da toxoplasmose congênita em Porto Alegre

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Congenital toxoplasmosis is associated with considerable morbidity when untreated.<sup>1–10</sup> From the time of the discovery of *T. gondii*-specific IgM in infants,<sup>11</sup> establishing the diagnosis of this infection has included the detection of *T. gondii*-specific IgM antibodies in serum of the newborn infant. However, whether this differs and the robustness of this test in different populations and regions has not been defined. Lago, Oliveira, and Bender describe their experience with the presence of *T. gondii* IgM in sera obtained from congenitally infected infants whose mothers were tested prenatally or in which only the infants themselves were tested in the newborn period at a screening program.<sup>12</sup> They also noted the duration that the anti-*T. gondii* IgM could still be detected in sera from infants with congenital toxoplasmosis, in a carefully performed and well-described study. The investigators used an IgM enzyme linked fluorescent assay (ELFA) (BioMérieux - Marcy l'Etoile, France) to detect *T. gondii*-specific IgM in serum and a fluorometric

enzyme immunoassay (FEIA) (iLabSystems - Helsinki, Finland) to detect *T. gondii* antibody in serum eluted from filter paper.

These investigators described both the utility and limitations of testing for *T. gondii*-specific IgM in sera of newborn infants with congenital toxoplasmosis in their region. They also highlight the circumstances in which the diagnosis can be missed, when this test is relied on exclusively. A careful characterization of this cohort of infants is also presented. There are three missing sets of information that would help with full interpretation of their data: (1) specifics of treatment; (2) the reason(s) for the long time lag between finding a positive IgM antibody and initiating treatment for the group of infants diagnosed with newborn screening, and (3) clarification of why only ultrasound of the brain was used without brain computed tomography for some infants, and how many these were, since computed tomography is more sensitive for the detection of intracerebral calcifications.

This study<sup>12</sup> took place in Porto Alegre, in Rio Grande do Sul, Brazil, from 1998 to 2009, and involved 65 infants. Inclusion criteria for the study were: routine maternal or newborn serologic screening; diagnostic confirmation with persistent IgG anti-*T. gondii* at age at 12 months or later; and screening for Toxo-IgM in the newborn period. They calculated the frequency of positive Toxo-IgM, and of cases identified by newborn screening that were excluded. They excluded newborns whose age when Toxo-IgM results became negative was not ascertainable and patients with negative Toxo-IgM.

DOI of original article:

<http://dx.doi.org/10.1016/j.jped.2013.12.006>

☆ Please cite this article as: McLeod R. Utility and limitations of *T. gondii*-specific IgM serum antibodies in the diagnosis of congenital toxoplasmosis in Porto Alegre. J Pediatr (Rio J). 2014;90:329–31.

☆☆ See paper by Lago et al. in pages 363–9.

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<http://dx.doi.org/10.1016/j.jped.2014.04.001>

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Among the 28 patients identified through maternal screening, 23 newborns had positive Toxo-IgM (82.1%; 95% CI: 64.7-93.1%). When they added 37 patients identified by neonatal screening, Toxo-IgM was positive in the first month of life in 60 patients. It was possible to identify when the result became negative in 51 of these infants. In 19.6% of patients, these antibodies were already negative at 30 days of life; and in 54.9%, at 90 days. Among the 65 patients included in the study, 40 (61.5%) had some clinical alteration. Possible reasons for the negative results could be early infection and resolution of production of IgM; maternal suppression of IgM production; and testing too close to the time of acquisition of infection, so that production of IgM had not yet occurred. Differences in treatment could also have altered results.

The authors of this work demonstrate that the test is useful, but they also note that even when tested using serologic methods with high sensitivity, up to one-third of infants with congenital toxoplasmosis may be negative for Toxo-IgM in serum at birth. Thus, presence of IgM specific for *T. gondii* is helpful, but its absence does not exclude the congenital infection. Therefore, they make the important point that if there is a suspicion of infection, the serologic screening should continue during the first year of life.

Furthermore, in cases of maternal infection that occurred very close to the time of delivery, newborns can show positive serology for toxoplasmosis a few days or weeks after birth. Thus, retesting is needed in the first month of life in that setting. This is a second important point for clinical care of such infants.

The period of positivity for Toxo-IgM was also not consistent for all such infants. Infected children with positive Toxo-IgM in newborn screening may already be negative at the time of confirmatory testing. Thus, such testing should not be initially regarded as false positivity for the screening test. This is a point worth emphasizing for the clinical care of such infants. Without clarification of how mothers during gestation and infants were treated, the time interval for IgM specific for *T. gondii* to remain positive is difficult to interpret. From the information in the article, the reason for the time lag to treatment for those infants whose congenital toxoplasmosis was detected with newborn screening as opposed to maternal screening is not clear. It is noteworthy that Desmonts and Couvreur found that the first month of life was a postnatal time when it was possible to isolate parasites from blood.<sup>13</sup> Thus, it is noteworthy that the lag in time to treat was on average this first month in the data presented by Lago et al.<sup>12</sup> Nonetheless, the same observations in this paper allowed for determination of the persistence of IgM specific for *T. gondii*, and provide evidence that it is important not to discontinue monitoring of infants with suspected congenital toxoplasmosis for synthesis of *T. gondii* specific IgG when there is a negative Toxo-IgM result.

The careful description by Lago et al. of IgM specific for *T. gondii* in congenitally infected children born in Porto Alegre also presents how this infection currently is manifested and managed in that city, where the incidence of this infection is quite high. The high incidence of retina and/or central nervous system findings in infants with congenital toxoplasmosis in Belo Horizonte, Minas Gerais, Brazil<sup>14</sup> is also found to be similar in Porto Alegre in the present study. The incidence of active retinitis was not as high as Vasconcelos-Santos et al.

reported for the Belo Horizonte/Fiocruz cohort, where 73% of the newborn infants detected by screening had active chorioretinitis. There was a trend toward a lower number of infants having *T. gondii* specific IgM when there was prenatal screening and treatment (specific treatment not specified) as has been demonstrated by Couvreur and Desmonts,<sup>13</sup> but that did not reach statistical significance in the Porto Alegre cohort. It is not clear whether this reflects the type or timing of treatment, or something about the parasite. In the United States, where there are a variety of different genetic types of parasites, prenatal diagnosis and treatment appeared to improve outcomes for all of them, and this did not vary by parasite type.<sup>15</sup> This improvement in outcomes is similar to that described in France.<sup>16-20</sup>

This work demonstrates the benefit and utility of diagnosis and initiation of treatment in a pre-natal and neonatal screening program in Porto Alegre. The finding that testing at birth with the IgM assay (ELFA, BioMérieux) specific for *T. gondii* infection aids in the diagnosis of congenital toxoplasmosis in Porto Alegre is useful. However, it is important also to note that the absence of *T. gondii*-specific IgM antibody does not exclude the infection. Thus, an important caveat is that such testing should not prevent subsequent antibody testing to make the diagnosis by later production of IgG antibody, when this infection is suspected, as such negative tests can occur in a number of settings and for a number of distinct reasons.

## Conflicts of interest

Dr. McLeod is chairperson of a committee to formulate diagnostic, management, and treatment guidelines for the IDSA; president of the Toxoplasmosis Research Institute, a 501c3 foundation to promote research, education, and care for those with toxoplasmosis and related diseases; holds various NIH grants; and is Director of the Toxoplasmosis Center at the University of Chicago.

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